PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WO 564	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/50225	International filing date *(day/month/year)* 13.06.2003	Priority date *(day/month/year)* 14.06.2002
International Patent Classification (IPC) or both national classification and IPC C07D417/06		
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.01.2004	04.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Allard, M Telephone No. +31 70 340-2002

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50225

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-21, 24-175	as originally filed
22, 23	received on 29.10.2003 with letter of 28.10.2003

Claims, Numbers

1 (part), 2, 8 (part), 9-25	as originally filed
1 (part), 3-7, 8 (part)	received on 29.10.2003 with letter of 28.10.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 21 (as to industrial applicability only)

   because:

   ☒ the said international application, or the said claims Nos. 21 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-7, 12-25
	No:	Claims	1-4, 8-11
Inventive step (IS)	Yes:	Claims	5-7, 12-25
	No:	Claims	1-4, 8-11
Industrial applicability (IA)	Yes:	Claims	1-20, 22-25
	No:	Claims	-

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: DATABASE CHEMCATS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 2002:2290627 XP002218003 & 'Exploratory Library (Catalog)' 21 January 2002 (2002-01-21) , AMBINTER

D2: DATABASE CHEMCATS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 2002:2290629 XP002218005 & 'Exploratory Library (Catalog)' 21 January 2002 (2002-01-21) , AMBINTER

D3: DATABASE CHEMCATS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 2002:2290615 XP002218009 & 'Exploratory Library (Catalog)' 21 January 2002 (2002-01-21) , AMBINTER

D4: WO 01 47920 A (APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.) 5 July 2001 (2001-07-05)

Re Item I

Basis of the opinion

The 2nd, 6th and 10th compounds excluded by proviso in the application as originally filed are no longer excluded in the newly filed claims and description: this clearly extends the scope of the claims and description beyond the application as originally filed.

Re Item III

Non-establishment of opinion with regard to industrial applicability

Claim 21 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step

or industrial applicability; citations and explanations supporting such statement

Novelty (Article 33(2) PCT)

D1-D3 disclose compounds affecting the novelty of claims 1-4 and 8-11.

The subject-matter of claims 5-7 and 12-25 is not disclosed in the available prior art and is therefore novel.

Inventive step (Article 33(3) PCT)

The subject-matter of claims 1-4 and 8-11 which is not novel does not offer a basis for acknowledging an inventive step.

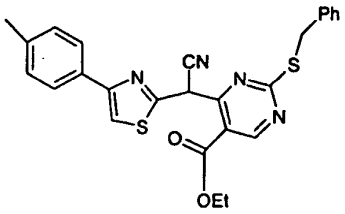
Concerning the novel subject-matter of claims 1-4 and 8-11 on the one hand, and the subject-matter of claims 5-7 and 12-25 on the other hand, an inventive step can be acknowledged for the provision of protein kinase inhibitors further to those disclosed in the closest prior art D4, which are not obvious with regard to the teachings of the prior art.

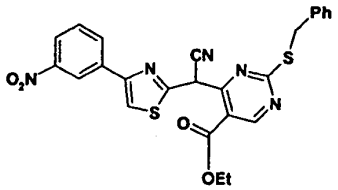
Industrial applicability (Article 33(4) PCT)

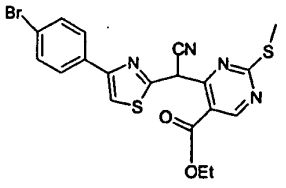
The compounds, uses and processes of claims 1-20 and 22-25 are applicable in the pharmaceutical industry.

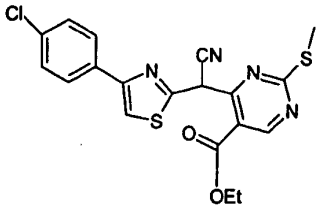
R^2 is selected from the group comprising or consisting of hydrogen, sulfonyl, amino, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, wherein said alkyl, alkenyl, alkynyl chains may be interrupted by a heteroatom selected from N, O or S, aryl, heteroaryl, saturated or unsaturated 3-8-membered cycloalkyl, heterocycloalkyl, wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl groups may be fused with 1-2 further cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, an acyl moiety, C_1-C_6-alkyl aryl, C_1-C_6-alkyl heteroaryl, C_1-C_6-alkenyl aryl, C_1-C_6-alkenyl heteroaryl, C_1-C_6-alkynyl aryl, C_1-C_6-alkynyl heteroaryl, C_1-C_6-alkyl cycloalkyl, C_1-C_6-alkyl heterocycloalkyl, C_1-C_6-alkenyl cycloalkyl, C_1-C_6-alkenyl heterocycloalkyl, C_1-C_6-alkynyl cycloalkyl, C_1-C_6-alkynyl heterocycloalkyl, alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkyl carboxy, C_1-C_6-alkyl acyl, aryl acyl, heteroaryl acyl, C_3-C_8-(hetero)cycloalkyl acyl, C_1-C_6-alkyl acyloxy, C_1-C_6-alkyl alkoxy, C_1-C_6-alkyl alkoxycarbonyl, C_1-C_6-alkyl aminocarbonyl, C_1-C_6-alkyl acylamino, acylamino, C_1-C_6-alkyl ureido, C_1-C_6-alkyl carbamate, C_1-C_6-alkyl amino, C_1-C_6-alkyl ammonium, C_1-C_6-alkyl sulfonyloxy, C_1-C_6-alkyl sulfonyl, C_1-C_6-alkyl sulfinyl, C_1-C_6-alkyl sulfanyl, C_1-C_6-alkyl sulfonylamino, C_1-C_6-alkyl aminosulfonyl, hydroxy or halogen,

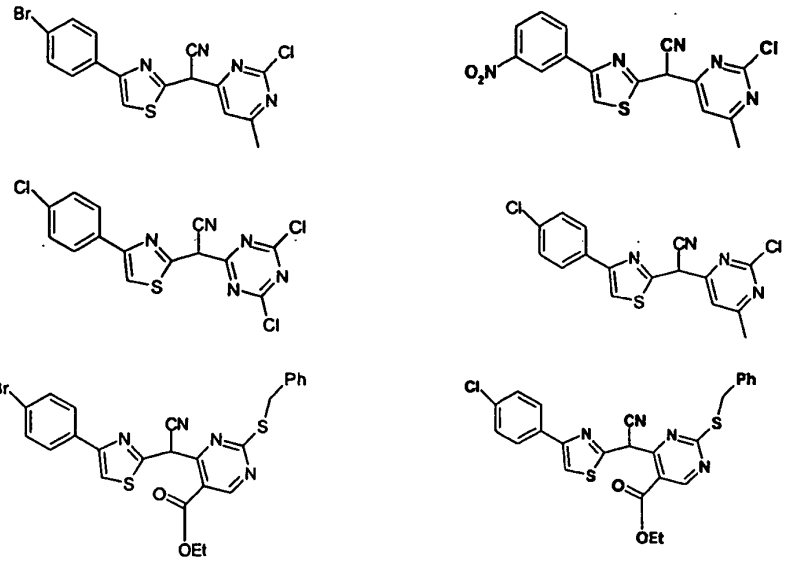
with the proviso that the following compounds are excluded :











2. Azole derivatives according to claim 1 wherein A is a pyrimidinyl group.

3. Azole derivatives according to claim 1 or 2 wherein R^0 is hydrogen.

4. Azole derivatives according to any of claims 1 to 3 wherein X is S.

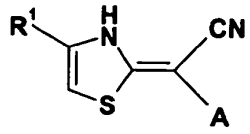
5. Azole derivatives according to any of claims 1 to 4 wherein R^2 is -NHR^4, with R^4 being a straight or branched C_1-C_6 alkyl which may be substituted by C_3-C_8-cycloalkyl, heterocycloalkyl, aryl, heteroaryl, amino, alkoxycarbonyl, acylamino, diacylamino.

6. Azole derivatives according to claim 5 wherein R^4 is a straight or branched C_2-C_4 alkyl group substituted with a heteroaryl or heterocycloalkyl group.

7. Azole derivatives according to claim 6 wherein said heteroaryl or heterocycloalkyl group is selected from a pyridyl, triazolyl or 2-pyrrolidinone.

8. Azole derivatives according to any of the preceding claims wherein R^1 is (C_3-C_8)-cycloalkyl, (C_3-C_8)-heterocycloalkyl, aryl or heteroaryl group which may be

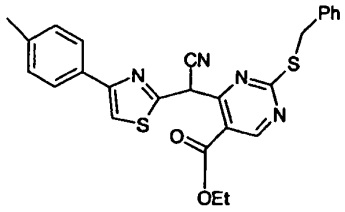
An even more specific embodiment according to the invention relates to compounds of the following formula (I') :

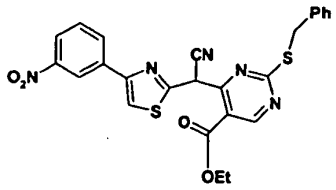


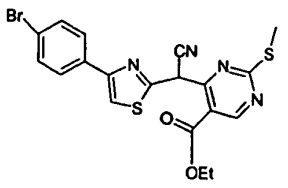
(I')

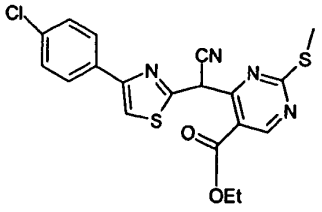
R^1 is an unsubstituted or substituted phenyl or or a straight or branched C_1-C_6 alkyl, or a halogen, A is a pyrimidinyl group which may be substituted with R^2 wherein R^2 is halogen or -NHR^4 in which R^4 is an unsubstituted or substituted straight or branched C_1-C_6 alkyl group which may be substituted with an unsubstituted or substituted pyridyl group.

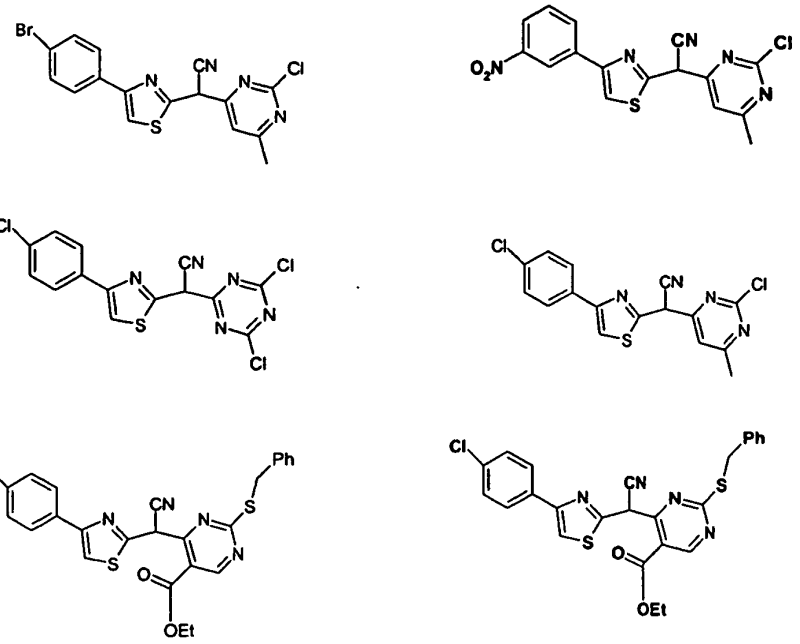
The following compounds appear to be not novel as they are listed in a commercial library ("Explorarory Library", Ambinter, 21.1.2002):











No medical use and no biological activity is disclosed for the above compounds, though.

Specific azole derivatives according to formula (I) are :

(2-chloropyrimidin-4-yl)-(4-ethyl-3H-thiazol-2ylidene)-acetonitrile

[4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene](2-chloropyrimidin-4-yl)acetonitrile

(2-chloropyrimidin-4-yl)(4-phenyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(2-chloropyrimidin-4-yl)(4-methyl-1,3-thiazol-2(3H)-ylidene)acetonitrile

(2-chloropyrimidin-4-yl)[4-(4-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

ethyl-2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate

methyl-2-[(2-chloropyrimidin-4-yl)(cyano)methylene]-2,3-dihydro-1,3-thiazole-4-carboxylate

(2-chloropyrimidin-4-yl)[4-(3-methoxyphenyl)-1,3-thiazol-2-yl]acetonitrile

(2-chloropyrimidin-4-yl)[4-(2-methoxyphenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile

(2-chloropyrimidin-4-yl)[4-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene]acetonitrile